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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/684,134

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Hal S. Padgett

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EXAMINER

SHAW, AMANDA MARIE

ART UNIT

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1634

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/684,134	Applicant(s) PADGETT ET AL.	
	Examiner AMANDA SHAW	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4,5 and 7-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4,5 and 7-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 August 2007 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) ☒ Information Disclosure Statement(s) (PTO/SB/08) | 5) ☐ Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>5/1/2008</u> . | 6) ☐ Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 1, 2008 has been entered.

Claims 1-2, 4-5, and 7-12 are currently pending. Claims 1 and 7-10 have been amended.

Declaration

2. The declaration filed on May 1, 2008 under 37 CFR 1.132 is sufficient to overcome the rejections made under 35 USC 103(a) in sections 8 and 9 of the Office Action of November 1, 2007 reference. Specifically the Applicants provided evidence that combining the T4 endonuclease VII of Mashall with the cellular DNA repair system of Arnold would have produced an inoperative invention. However new rejections are set forth below.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-5, 7-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2, 4-5, 7-12 are indefinite over the recitation of the phrase "cleaving...with an effective amount of mismatch directed strand cleavage activity". This phrase is considered indefinite because one cleaves with an enzyme having mismatch directed strand cleavage activity.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 4-5, and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (US Patent 5571676) in view of Oleykowski (Nucleic Acids Research 1998).

Regarding Claim 1 Shuber teaches a method that comprises (a) hybridizing a DNA sample with one or more genetic alterations with a second DNA sample that does not contain the alteration(s) to form heteroduplex DNA; (b) cleaving one strand of the heteroduplex so that a single-stranded gap forms across the site of the alteration(s); and (c) treating the cleaved heteroduplex with a DNA polymerase in the presence of dideoxynucleotides to determine the nucleotide sequence across said gap (Col 4, lines 30-40, Col 8, line 50 to Col 9, line 16, and Claim 1). Thus Shuber teaches preparing at least one heteroduplex between at least two parent polynucleotides, cleaving at least one polynucleotide strand, and replacing at least one nucleotide at or near the cleavage step.

Shuber does not teach a method wherein the cleaving step is performed with an effective amount of a mismatch endonuclease that cleaves within six nucleotides 3' of a mismatch site.

However Oleykowski teaches a method wherein a cleaving step is performed with CEL I. In the instant case CEL I is considered a mismatch endonuclease that cleaves within six nucleotides 3' of a mismatch site because CEL I incises on the 3' side of the mismatch site in one of the two DNA strands in a heteroduplex (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Shuber by using CEL I to

cleave the heteroduplex containing mismatches as suggested by Oleykowski particularly since Oleykowski teaches that CEL I can detect 100% of the sequence variants present, including deletions, insertions and missense alterations. Further it would have been obvious to use CEL I because the substitution of one cleavage agent for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Thus the combination of Shuber and Oleykowski would result in the production of one polynucleotide strand that has a nucleotide sequence not identical to either of the at least two parent polynucleotides or the complementary sequence of the at least two parents.

Regarding Claims 4 and 5 Shuber teaches that five primer sets were used to simultaneously amplify relevant regions of exons 4, 10, 20, and 21 of the cystic fibrosis transmembrane conductance regulator gene (CFTR). The amplified DNA was used to form the heteroduplex (Example 1). In the instant case the heteroduplex of Shuber is being interpreted as containing the CFTR gene. It is noted that the claims do not require that the heteroduplex contains an entire gene. Further the heteroduplex of Shuber is being interpreted as a genome. It is noted that the claims do not require that the heteroduplex is an entire genome.

Regarding Claim 7 Shuber teaches a method that comprises (a) hybridizing a DNA sample with one or more genetic alterations with a second DNA sample that does not contain the alteration(s) to form heteroduplex DNA; (b) cleaving one strand of the heteroduplex so that a single-stranded gap forms across the site of the alteration(s); and (c) treating the cleaved heteroduplex with a DNA polymerase in the presence of

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dideoxynucleotides to determine the nucleotide sequence across said gap (Col 4, lines 30-40, Col 8, line 50 to Col 9, line 16, and Claim 1). Further Shuber teaches that five primer sets were used to simultaneously amplify relevant regions of exons 4, 10, 20, and 21 of the cystic fibrosis transmembrane conductance regulator gene (CFTR). The amplified DNA was used to form the heteroduplex (Example 1). Thus Shuber teaches a method wherein at least two different heteroduplexes are formed among at least three parent polynucleotides, cleaving at least one polynucleotide strand, and replacing at least one nucleotide at or near the cleavage step.

Shuber does not teach a method wherein the cleaving step is performed with an effective amount of a mismatch endonuclease that cleaves within six nucleotides 3' of a mismatch site.

However Oleykowski teaches a method wherein a cleaving step is performed with CEL I. In the instant case CEL I is considered a mismatch endonuclease that cleaves within six nucleotides 3' of a mismatch site because CEL I incises on the 3' side of the mismatch site in one of the two DNA strands in a heteroduplex (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Shuber by using CEL I to cleave the heteroduplex containing mismatches as suggested by Oleykowski particularly since Oleykowski teaches that CEL I can detect 100% of the sequence variants present, including deletions, insertions and missense alterations. Further it would have been obvious to use CEL I because the substitution of one cleavage agent for another would have yielded predictable results to one of ordinary skill in the art at the

time of the invention. Thus the combination of Shuber and Oleykowski would result in the production of one polynucleotide strand that has a nucleotide sequence not identical to either of the at least three parent polynucleotides or the complementary sequence of the at least three parents.

Regarding Claim 8 Shuber teaches that five primer sets were used to simultaneously amplify relevant regions of exons 4, 10, 20, and 21 of the cystic fibrosis transmembrane conductance regulator gene (CFTR). The amplified DNA was used to form the heteroduplex (Example 1). In the instant case since five heteroduplexes are used in the method of Shuber at least 5 variant polynucleotides would be formed. In the instant case 5 is being interpreted as a plurality

6. Claims 2 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (US Patent 5571676) and Oleykowski (Nucleic Acids Research 1998) and in further view of Arnold.

The teachings of Shuber and Oleykowski are presented above.

Regarding Claim 2 the combined references do not teach a method wherein the heteroduplex is circular.

However Arnold teaches a method wherein the polynucleotides forming a heteroduplex are circular (Page 13, lines 3-4).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Shuber and Oleykowski by using heteroduplex polynucleotides as suggested by Arnold. Since all of the claimed

elements were known in the prior art one skilled in the art could have combined the claimed elements and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Regarding Claims 9 and 10 the combined references do not teach further screening or selecting the population of variants for a desired functional property. Regarding Claim 11 the combined references do not teach converting said polynucleotide to RNA before screening or selecting. Regarding Claim 12 the combined references do not teach translating said variant to produce a polypeptide wherein screening or selecting is performed on polypeptide.

Arnold teaches a method comprising screening or selecting the population of variants for a desired functional property (Page 9, lines 30-31). Arnold teaches that the variant polynucleotides can be converted to RNA and be translated prior to screening and selecting. Specifically Arnold teaches that the variant polynucleotides (DNA) as well as their expression products or secondary metabolites produced by their expression products are isolated and screened for the desired property (Page 18, lines 13-15). In order for the expression products to be analyzed, the DNA would have had to be converted to RNA and then translated.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Shuber and Oleykowski by further screening the population of variants for a desired function as suggested by Arnold. One of skill in the art would have been motivated to screen the polynucleotides for a desired function to determine how and if the variants change the function of the

wild type polynucleotide. Further one would have been motivated to convert the variants to RNA and then to protein in instances where the desired function is that of for example of an enzyme in order to see if the enzyme encoded by the protein actually has increased catalytic activity.

Conclusion

7. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Amanda M. Shaw
Examiner
Art Unit 1634

/Carla Myers/
Primary Examiner, Art Unit 1634